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The use of coronary artery calcium scanning in detection and risk stratification of coronary artery disease

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ABSTRACT

Coronary artery calcium (CAC) scan can be obtained using chest computed tomography, with no use of contrast agents, and with a relatively low radiation exposure. The mere absence of calcium is associated with a good prognosis in asymptomatic subjects and in patients at low to medium risk of coronary artery disease. CAC can be quantified in different ways, with higher scores being associated with a higher cardiovascular risk. CAC carries both diagnostic and prognostic information over and above that determined by classical risk factors. This paper presents the overview of the current use of CAC scanning, its advantages and limitations, as well as potential future applications.

Contents

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Introduction

Coronary artery calcium (CAC) deposits are almost entirely due to atherosclerosis. It is, therefore, logical to expect that CAC measurement may be a useful tool in excluding or confirming the presence of coronary artery disease (CAD) in subjects with or without symptoms, but with no proven cardiovascular disease (CVD).

CAC can be reliably assessed by means of computed tomography (CT).

By the widely accepted definition, coronary calcium is present when the threshold of 130 Hounsfeld units is exceeded in at least 3 adjacent pixels [1].

Although multiple quantification criteria can be applied, the Agatston score, reflected in Agatston units (AU), and determined by the product of the calcified plaque area and maximal calcium lesion density is most commonly used [2].

The lack of coronary calcium deposits does not exclude the presence of obstructive changes in the coronary tree, especially in patients aged <45 years. For example, in one study including a group of 166 subjects with intermediate CAD probability and CAC score (CACS) = 0 AU, a non-significant stenosis was present in 10%, and a significant one in 2% of patients [3]. In another study [4] no coronary lesions were found in asymptomatic subjects, while 0.8% of those with symptoms had soft obstructive changes. When it comes to high-risk groups, like patients with symptoms suggestive of ischemia who have clinical indications to invasive coronary angiography, the prevalence of obstructive stenoses in those with CACS = 0 may be as high as 19% [5].

In the MESA study, a positive CAC was a better predictor of incident coronary events than carotid plaque presence and increased carotid intima-media thickness [6].

In general, patients with no detectable CAC are at very low risk of CV events. The presence of CAC increases the risk in an incremental mode. In long-term, the relative risk of death or MI is about threefold higher in patients with CACS 1–10 as compared to those with negative CAC. A similar difference is seen between individuals with CACS > 100 and those with CACS values between 1 and 99 (RR 3.20; 95% CI 1.17–8.71) [7].

Traditionally, people with positive CAC, with the score values 1–100, 100–400 and >400 AU, are considered to be at low, intermediate and high risk of both ischemia and CV events. CACS values >400 AU can be regarded as a CAD equivalent, with a 10-year event rate of over 20%, even in asymptomatic patients [1].

However, CACS interpretation should always take into account the clinical context, including at least the symptoms and age.

Measurement of CAC volume and density may have an added value to the CACS measured in the Agatston units. In a large cohort of patients in the MESA study, followed for the median of 7.6 years, CAC volume showed an independent positive association with CAD events, while CAC density was associated with an independent inverse association at any level of CAC volume [8]. Therefore, CAC density should probably be taken into consideration in risk evaluation.

The American appropriateness use criteria for CT scanning [9] give a limited mention to the non-contrast coronary CT as a stand-alone diagnostic method. CACS assessment is deemed appropriate in patients with positive family history of premature CAD, and in asymptomatic subjects with no known CAD being in the intermediate risk group, as assessed by age, sex and symptoms.

The ESC guidelines on the management of patients with stable CAD [10] underscore that the amount of calcium correlates with the extent of atherosclerotic changes, but the correlation with the presence of hemodynamically significant stenosis is rather poor. In practice, this means that high CACS is not always associated with a significant coronary stenosis, and – on the other hand – the CACS = 0 cannot exclude CAD, especially in young patients presenting with an acute coronary syndrome.

A comprehensive overview of the pathogenesis and prognostic implications of coronary artery calcification can be found in the paper by Madhavan et al. [11].

CAC in asymptomatic subjects

In a systematic review including more than 85,000 asymptomatic subjects with CAC score = 0, only 0.56% experienced a cardiovascular event during a mean follow-up of 51 months [12]. Therefore, the absence of CAC was associated with a very low risk of cardiovascular events (0.13% per year. The absence of CAC had a 93–99% negative predictive value for detection of significant coronary lesions on invasive angiography.

Even low but positive CACS seem to be associated with an increased risk as compared to those with no CAC in asymptomatic subjects. In a subpopulation of patients from the MESA study with CACS 0–10 AU, in the analysis adjusted for age, gender, race and CAD risk factors, the subjects with CACS 1–10 AU showed a threefold increase in risk of hard CAD events (CAD death or non-fatal myocardial infarction) compared to those with CACS = 0 [13].

Higher CACS value tend to bear an incremental risk of CAD events.

Al Rifai et al. [14] followed-up a group of 4234 asymptomatic subjects with CAC score ≥400 AU. Their mean age was 64 years, males constituted 65% of the group, and the median CAC score was 809. In multivariable analysis age, diabetes, smoking, increasing CAC score and dyslipidemia were associated with 1-year all-cause mortality (HR for CAC 1.33; 95% CI 1.11–1.56). Diabetes and smoking showed the strongest association (respective HR 2.62 and 2.42), suggesting that in the presence

of extensive coronary calcification, these risk factors may be most important triggers of acute coronary events. Moreover, in the subgroup of 781 individuals in whom hypertension was the only risk factor, a positive CAC, irrespective of the numerical value, was associated with an almost fivefold increase in the risk of death (HR 4.68 [95% CI: 2.22–9.87]) as compared to those with no CAC.

In a recent subanalysis of the MESA study [15] CAC values proved to be additive to the information on hyperlipidemia. Subjects with CACS = 0 had cardiovascular event rates of 2.7–5.9 per 1000 person-years, while in those with CACS ≥ 100 the event rates were 22.7–29.5 per 1000 person-years, irrespective of the presence and severity of lipid abnormalities.

CAC proved to be a useful predictor of CV events in clinically healthy subjects with a positive family history of premature coronary heart disease [16]. Relative to CACS = 0, adjusted ratios for hard cardiovascular events were significantly increased in those with CACS values of 100–399 and ≥400 (HR 2.45; 95% CI 1.31–4.58, and 2.80; 95% CI 1.44–5.43, respectively). In subjects with CACS 1–99, a similar, non-significant trend was observed. Again, in this study, CAC appeared to be a robust marker of absolute and relative risk of CV events.

Diabetes mellitus and some inflammatory disorders, such as, e.g. ankylosing spondylitis and systemic lupus, can accelerate coronary atherosclerosis. In this setting, early detection of CAC is of special importance, since it may trigger introduction of preventative measures at an early stage of CAD.

CAC in symptomatic subjects

The data on the value of CAC assessment in symptomatic patients are scarce.

In a large systematic review, symptomatic subjects with CACS = 0 had a low probability of an event (1.8% during a 42-month follow-up, or 0.51% per year) [12].

Sosnowski et al. [17] examined a group of 362 consecutive symptomatic subjects aged 45 years and less, and correlated the presence of CAC with the risk factors, such as gender, body mass index (BMI), smoking, blood pressure, lipids concentration, diabetes, physical activity and positive family history. Almost 18% of all subjects had a positive CAC value. Apart from male gender and the presence of diabetes, traditional risk factors were unable to identify patients with premature coronary atherosclerosis. Presence of at least 4 risk factors was associated with more frequent positive CAC (26% vs 16%; $p < 0.05$). CAC measurement can be justified in young symptomatic people with a large number of risk factors, and especially in males with diabetes.

In the setting of an acute coronary syndrome, the absence of CAC, combined with undetectable high-sensitivity troponin levels, may be useful in identifying patients who do not need further evaluation [18].

It has been suggested that high CAC values are associated with higher complication rates in patients undergoing percutaneous coronary interventions [11]. Heavy calcifications are also linked to a worse coronary artery bypass surgery outcome, due to incomplete revascularization and higher likelihood of vein graft calcification [11].

It needs to be emphasized, however, that there are no data that CACS measurement would have any additional value over and above the data provided by invasive coronary arteriography.

Changes of CAC score over time

Among 3112 subjects with CACS = 0 at baseline, with mean age of 58 years (64% female) included in the MESA study, 1125 (36%) developed a positive CAC score at the follow-up ranging from 2 to 10 years. New CAC was generally present in one artery only, and the score was low (median 7.1). Less than 5% of patients had the CAC score >100 at the repeated scan. Mean time to new calcium detection was 6.1 years [19]. These findings suggest that using repeated CAC assessment, coronary atherosclerosis can be detected in an early stage, when aggressive preventive strategies may decrease the life-time risk of CV events.

Based on the data from Heinz Nixdorf Recall Study, Erbel et al. [20] suggest that progression of coronary calcification is inevitable and predictable. They found that CACS tends to exponentially increase with age, and the increase is, to some extent, also related to blood pressure, lipid-lowering medication, diabetes and smoking. The classical CV risk factors, however, had a limited influence on the CACS changes. In an accompanying editorial Budoff makes the point that formation of coronary calcium deposits may show different dynamics, and that the individual progression rate may be a strong predictor of cardiovascular events [21]. This view is corroborated by the data from the MESA study, showing that in patients in whom the increase in CACS exceeded 300 AU, the likelihood of incident hard coronary events over 7.6-year follow-up was over 6 times higher than in those with no progression [22].

Recommended intervals between the baseline and follow-up CAC measurements may vary, depending on the clinical setting. It is, however, believed, that asymptomatic subjects with the initial CACS = 0 AU do not need a repeat study for at least 4 years [1].

The effect of treatment on CAC

The effect of treatment on CAC has not been adequately studied. There are no convincing data that any treatment is associated with the decrease in CACS. Although statins are known to lower clinical events, their use may be associated with an increase rather than decrease of CACS. In a post hoc patient-level analysis of 8 randomized trials, Puri et al. [23] found that statins promote coronary atheroma calcification, which may underlie plaque stabilization and, at least partially, explain their clinical benefit.

Should CAC assessment be supplemented with CT angiography?

CAC evaluation can be considered as a stand-alone examination or in conjunction with CT coronary angiography. The knowledge of coronary anatomy is essential in a number of

clinical settings [9]. Whether CT angiography can provide clinically relevant diagnostic and prognostic information of the top of CAC measurement in subjects with no apparent CAD remains a matter of controversy.

In the FACTOR-64 trial [24], 900 patients with diabetes but no apparent cardiovascular disease were randomized to CT angiography or usual care. Standard or aggressive care were chosen based on the CT angiography findings. The mean follow-up was 4 ± 1.7 years. No significant difference in the composite outcome including all-cause mortality, non-fatal MI or unstable angina requiring hospitalization, was observed between CT-angiography-driven treatment and the control group (HR 0.8, 95% CI 0.49–1.32; $p = 0.38$). Therefore, this study did not support the CT angiography screening in this asymptomatic, but high-risk population.

On the contrary, in the CONFIRM registry [25] including 8627 symptomatic patients without known CAD, who underwent both CAC assessment and CT angiography, the CT angiography was shown to have an incremental discriminatory power to identify patients at risk of death or MI.

A significant progress has been made in limiting radiation exposure during coronary CT. It is likely that even with coronary CT angiography, radiation exposure may be lower than 0.5 mSv [26]. If this becomes reality, the applicability of both CAC measurement and CT angiography will likely increase.

Advantages and limitations of CAC assessment

Benefits and problems related to CAC evaluation, as well as the current and potential future application of CAC scanning have been excellently addressed by Hecht in his recent review paper [1]. Table 1 lists the most important benefits and limitations of CAC scanning.

Potential use of CAC

The role of CAC scoring in the current guidelines appears to be underplayed. The indications to assess the CAC with no visualization of coronary arteries should be possibly extended to include the indications listed in Table 2.

The value of CAC measurement must be considered in the context of multimodality imaging. In a cohort of 988 asymptomatic or symptomatic low-risk patients without prior CAD, followed-up for a median of 6.9 years, relative value of Framingham risk score, CACS, exercise tolerance test (ETT), and stress myocardial perfusion SPECT results were compared as predictors of cardiac events, defined as a composite of cardiac death, non-fatal MI and the need for coronary revascularization [27]. The cardiac event rate was 1.6% per year. In this study, CACS significantly improved long-term risk stratification beyond the Framingham risk score. ETT and SPECT results, which supports the use of CACS as a first-line test for the assessment of long-term risk is this patient group.

In patients with heart failure, it is important to differentiate between those with the ischemic vs non-ischemic etiology. CACS, in most instances accompanied with CT angiography, can serve this purpose, avoiding the need of invasive coronary artery anatomy assessment.

Radiation exposure of CAC scoring (<1 mSv) is comparable to mammography, which is widely used as a screening method to detect breast cancer [28]. In this context, CACS measurement may become an acceptable method to assess the likelihood of incident cardiovascular events at the population level. The definition of the cohort qualifying for screening remains to be established. SHAPE investigators propose to use it in women aged 55–75 and in men aged 45–75 years [29].

It has been also postulated that CAC measurement may be a useful tool to qualify patients at risk of CAD to the polypill preventive treatment [30]. This may be also true for more patient-tailored treatment with statins, ACE inhibitors or antiplatelet drugs.

Table 1 – Benefits and problems of coronary artery calcium scanning (modified after Hecht [1]).

Benefits
- Risk stratification superior to risk factors
- High net reclassification index
- Gatekeeper to functional testing
- Cost effectiveness
- Radiation exposure similar to mammography
Problems
- Absence of randomized trials

Table 2 – Current and potential indications for the CAC evaluation.

Current indications [7]
Initial risk assessment in:
- symptomatic subjects with no known CAD, being in the intermediate risk group
- patients with positive family history of premature CAD
Potential indications
- Longitudinal screening for CAC progression
- Establishing indications for preventive treatment
- Screening for CAC in symptomatic subjects with a large number of risk factors
- Exclusion of an acute coronary syndrome (in conjunction with troponin measurement)
- Exclusion of ischemic etiology in patients with heart failure
- Initial screening for CAC at the population level [29][a]

[a] According to Naghavi et al. [29], women aged 55–75 years and men aged 45–75 years may be considered.

Conclusions

The presence of calcium confirms coronary atherosclerosis and is associated with increased incidence of coronary events. The presence and extent of CAC tends to be a better predictor of future coronary events than the classical risk factors. However, the results of CAC scanning should be always interpreted in the clinical context, taking into account patient's age and the presence or absence of symptoms.

Clinical usefulness of CAC measurement is likely to increase in the future, especially with the advent of new techniques reducing radiation exposure.

Conflict of interest

No conflict of interest.

Ethical statement

I declare, on behalf of all authors that the research was conducted according to Declaration of Helsinki.

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